pH changes. Thus, no indefiniteness is imparted by these "pH" related phrases.

The claims, of course, encompass any single amphetamine base salt, or mixtures thereof, chiral, nonchiral, etc. Specific recitation in the specification and some claims of the "four amphetamine salts" in ADDERALL® referred to on page 4 of the specification is clearly not new matter since these are inherently incorporated by reference, e.g., in view of the passage at page 4, lines 15-17, e.g., from the package insert for ADDERALL®. *In re Hawkins*, 486 F. 2d. 579, 179 USPQ 163 (CCPA 1973). See the excerpt from the 1997 Physicians' Desk Reference.

The amended language and the new claims are supported by the specification. For instance, support for the lag time ranges may be seen at page 13, line 17 and page 6, lines 4-6. See also, *In re Wertheim*, 541 F. 2d 247, 191 USPQ 90 (CCPA 1976) and *In re Voss*, 557 F. 2d. 812, 194 USPQ 267 (CCPA 1977), establishing that subranges subsumed by a given range have a written description by virtue of the given range *per se*. Use of the term "base" in the claims clarifies that "amphetamine salt" does not have the broader meaning given at page 12, lines 19-23, but means salts of amphetamine base (page 12, line 20). Effective durations (e.g., at least 8 hours, for 12 hours) are supported at page 16, lines 1-8. The relationship between the plasma levels of the first and second doses is supported, e.g., in Figs. 1, 7 and 8.

New independent claims 47, 57, 67 and 95 recite a feature relating to the plasma curve of Figure 7, reference to which is necessary for definition of the concept involved. (See MPEP § 2173.05(s)). It is believed the applicability of the latter MPEP section was agreed to during the interview. It is also believed this recitation in essence meets the Examiners' recommendation that the claims reflect highly conventional plasma profile definitional parameters such as C_{max} and AUC (area under the curve). Recitation of a profile inherently defines AUC and C_{max}. These claims' references to "is substantially the same," are supported and interpreted by inherent reference to conventional standards employed by those of ordinary skill in the art, e.g., at FDA, in determining when plasma profiles are equivalent, taking into account dosage amounts.

Independent claim 19 recites, e.g., the features of a 2-6 hours lag time between two doses, a second release achieving a plasma level higher than that achieved previously by the first dose and a composition achieving an effective level for at least 8 hours without further administration.

It is believed these recitations achieve the Examiners' other recommendation that the claims reflect relative peak features such as the timing of each peak, the height of each peak and the durations involved.

The Examiner alleges two bases for lack of enablement. It is respectfully submitted that both are untenable under U.S. law.

First, patent specifications are presumptively enabling. In making an enablement rejection, it is incumbent upon the PTO to provide reasons or evidence to doubt the objective enablement of a patent specification or the accuracy of all statements made therein. *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (CCPA 1971). No such reasons or evidence has been established or even alleged. Even if an unpredictable technology were involved, the *Marzocchi* principle still fully applies. *In re Angstadt*, 537 F.2d 498, 190 USPQ 214 (CCPA 1976).

As for the Examiner's first allegation, applicants' specification provides more than sufficient guidance for a skilled worker to routinely make the formulations of the claims, e.g., to achieve the features recited in the claims, such as plasma concentration profiles/curves, plasma levels after second dosage release, lag times, efficacy durations, etc. Especially in this regard, see Figs. 7 and 8, Example 5 (page 19) and page 16, lines 1-8, of the specification. These show how plasma profiles and levels change with immediate dose/delayed dose features of the invention, such as different lag times. (Such times are disclosed in the figures as can be seen from the point in the curves at which the decreasing slope in the initial rising curve slope begins again to increase due to the release of the second pulse, e.g., approximately four hours in Fig. 7 and approximately 6.5 hours in Fig. 8.) The routineness of achieving the claimed subject matter under the guidance of the specification in no way implies obviousness as established below.

As for "what is required" to provide immediate and delayed release doses where recited, this feature of the claimed invention relies on fully conventional formulation principles, to which the Examiner even refers on pages 6 and 7 of the office action. Note the in-depth discussion in the specification of the preferred use of pulsatile/enteric technology to carry out the claimed invention. Also note the discussion on pages 3 and 4 thereof, by reference to prior art, of other techniques which can achieve immediate and delayed release formulations. Thus, this aspect of the Examiner's enablement rejection is also untenable and should be withdrawn.

The claimed invention is clearly not obvious in view of the cited '388 patent.

'388 is a "device" patent, in essence. It deals with how to make a device, e.g., capsule, which will open up and release whatever is in it at a prescribed time. It does this using osmotic techniques. It is disclosed as especially applicable to a two dose release system, where one dose is essentially immediately released and the other is delayed by the device. But no guidance at all is given regarding how any drug should be released, what time differentials should be used between the two doses (lag times), what the relative plasma levels should be for the two doses, what the durations of efficacy should be and certainly not what the plasma/concentration profiles/curves should look like. Perhaps, any of these features, once selected, can be achieved using the disclosed prior art device, but to render the claimed subject matter obvious the "desirability" of the feature must be given in the prior art. "Motivation" for the selections must be given in the prior art, as the Federal Circuit has consistently and insistently held.

> Before the PTO may combine the disclosures of two or more prior art references in order to establish *prima facie* obviousness, there must be some suggestion for doing so, found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art.
>
> Conspicuously missing from this record is any *evidence*, other than the PTO's speculation (if it be called evidence) that one of ordinary skill in the herbicidal art would have seen motivated to make the modifications of the prior art salts necessary to arrive at the claimed 2-(2'-aminoethoxy) ethanol salt. *In re Jones*, 958 F. 2d 347, 21 USPQ 2D 1941 (Fed. Circ. 1992).

However, '388 gives absolutely no such motivation, despite its bare inclusion of amphetamine sulfate in a long laundry list of applicable active ingredients, as the examiner notes. The specification of '388 may generally state that essentially any desired release features can be accommodated by its device, but it gives no hints of which features should be chosen for any drug. The drugs can be the same or different in each dose form (e.g., col. 10, lines 30-37, col. 11, lines 62-64, col. 13, (lines 52-56, etc.). When the device opens up, the contained active ingredients for delayed release will be exposed to the surrounding environment, but they can be contained therein in any possible formulation, e.g., fast release, slow release, etc. (col. 6, line 49

to col. 7, line 16). The same is true for the immediately released dosage form (col. 3, lines 34-36, etc.). (Contrary to the Examiner's allegation in paragraph 16 of the office action, col. 3, lines 25-51 of '388 refers to release of active agent formulation, not active agent *per se*). The second dose can begin release before or after the first release is completed (col. 11, lines 56-62, etc.). The device can be designed to stay in or pass through the stomach (col. 15). And so on. As can be seen, the possibilities are endless; no guidance is given of which features to select for any drug, let alone specifically for amphetamines.

The examples of '388 are no different. Examples 1-4 merely describe how to make devices and do not mention any active ingredients at all. Examples 5 and 6 (mentioned by the Examiner) test how long it takes various devices to open up in intestinal fluid, no active ingredient formulations being contained at all. Examples 7 and 8 do the same for devices containing cardizem pellets and cimetidine granules, respectively. But no details are given of the nature of how the pellets or granules release the active ingredients once the device opens up, i.e., slowly, quickly, controlled, sustained, etc. (Even if such information were given, it would provide no guidance as to amphetamines.) Finally, Example 9 is the only one with a two-dose device but, again, it describes only how to construct the device, contains no active agent formulation and provides none of the mentioned missing guidance.

Clearly, the obviousness rejections are untenable, the secondary reference merely providing the known fact that ADHD can be treated with amphetamines. No amphetamine "product" is described, as alleged. Much more than "mere optimization" is involved. The question is not whether '388 or other prior art can be used to achieve the features recited in the claims, but rather whether the claimed subject matter as a whole, including the release and profile features recited, is obvious, e.g., whether the prior art suggests to or motivates one of ordinary skill in the art to select such features. As can be seen above, this is not the case.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION

See page 3, fourth paragraph, please amend the specification to read as follows:

Tablets or capsules coated with a hydrophobic wax-surfactant layer, made from an aqueous dispersion of carnauba wax, beeswax, polyoxyethylene sorbitan monooleate, and hydroxpropyl methylcellulose have been used for rapid drug release after a predetermined lag time. ~~For example,~~ However, even though a two-hour lag time was achieved for the model drug theophylline at a higher coating level (60%), three hours were required for a complete release of theophylline after the lag time. (8)

See page 4, third paragraph, please amend the specification to read as follows:

~~ADDERAL®~~ ADDERAL® comprises a mixture of four amphetamine salts, dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate and amphetamine sulfate, which~~,~~ in combination, are ~~is~~ indicated for treatment of Attention Deficit Hyperactivity Disorder in children from 3-10 years of age. One disadvantage of current treatment is that a tablet form is commonly used which many young children have difficulty in swallowing. Another disadvantage of current treatment is that two separate dose are administered, one in the morning and one approximately 4-6 hours later, commonly away from home under other than parental supervision. This current form of treatment, therefore, requires a second treatment which is time-consuming, inconvenient and may be problematic for those children having difficulties in swallowing ~~table~~ tablet formulations.

IN THE CLAIMS:

Please amend the claims as follows:

19. (Amended) ~~A pharmaceutical~~ An orally administrable pharmaceutical composition comprising:

(a) an immediate release dosage form containing an amount of one or more ~~a mixture of pharmaceutically active~~ amphetamine base salts effective to treat ADHD in a human patient; and

(c) a delayed release dosage form containing an amount effective to treat ADHD in a human patient of one or more ~~a mixture of~~ amphetamine base salts,

wherein ~~after release of the~~ said ~~amphetamines~~ amphetamine base salts are released from the delayed release ~~dose~~ dosage forms beginning 2-6 hours after administration, after which release the maximum plasma concentration of the ~~amphetamines~~ amphetamine base salts reaches a level ~~reaches a maximum level that is~~ greater than any previous ~~the maximum~~ level ~~of the amphetamines plasma concentration that is~~ reached ~~during the period prior to release of amphetamines from the delayed release dose~~ after the beginning of said immediate release, and

wherein said composition is sufficient to maintain an effective level of amphetamine base salts in the patient over the course of at least 8 hours without further administration of amphetamine base salt.

27. (Amended) The composition of claim ~~23~~ 19 wherein the composition includes an amount of ~~amphetamines~~ amphetamine base salts to provide an effective level thereof in said patient ~~recipient~~ without further administration over a course of ~~eight~~ twelve hours.

35. (Amended) A composition ~~The process~~ of claim ~~30~~ 19 ~~wherein the pharmaceutical is~~ in the form of a capsule, said capsule including the immediate release ~~dose~~ dosage form and the delayed release ~~dose~~ dosage form.

42. (Amended) The composition of claim 19 wherein the ~~amphetamines are amphetamine bases~~ amphetamine base salts are dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate and amphetamine sulfate.

43. (Amended) The composition of claim ~~23~~ 75 wherein the ~~amphetamines~~ amphetamine base salts ~~are amphetamine bases~~ are dextroamphetamine sulfate.

dextroamphetamine saccharate, amphetamine aspartate monohydrate and amphetamine sulfate.

44. (Amended) The ~~process~~ composition of claim ~~30~~ 32 wherein the ~~amphetamines~~ amphetamine base salts ~~are amphetamine bases~~ are dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate and amphetamine sulfate.

45. (Amended) The ~~process~~ composition of claim ~~36~~ 35 wherein the ~~amphetamines~~ amphetamine base salts ~~are amphetamine bases~~ are dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate and amphetamine sulfate.

46. (Amended) The ~~process~~ composition of claim ~~40~~ 27 wherein the ~~amphetamines~~ amphetamine base salts ~~are amphetamine bases~~ are dextroamphetamine sulfate, dextroamphetamine saccharate, amphetamine aspartate monohydrate and amphetamine sulfate.